SOLICITATION, OFFER AND AWARD

1. THIS CONTRACT IS A RATED ORDER UNDER DPAS (15 CFR 700)	RATING	PAGE OF PAGES
▶		1 of 33

2. CONTRACT NUMBER	3. SOLICITATION NUMBER	4. TYPE OF SOLICITATION	5. DATE ISSUED	6. REQUISITION/PURCHASE NO.
	RFP NHLBI-HC-99-15	☐ SEALED BID (IFB) ☑ NEGOTIATED (RFP)	12/4/98	

7. ISSUED BY	CODE	8. ADDRESS OFFER TO *(If other than Item 7)*
National Heart, Lung, & Blood Institute, NIH Rockledge2, Room 6118 6701 ROCKLEDGE DR MSC 7902 BETHESDA MD 20892-7902		Review Branch, Division of Extramural Affairs National Heart, Lung, and Blood Institute, NIH Rockledge Building, Room 7091 6701 ROCKLEDGE DR MSC 7924 BETHESDA MD 20892-7924

NOTE: In sealed bid solicitations "offer" and "offeror" mean "bid" and "bidder"

SOLICITATION

9. Sealed offers in original and 25* copies for furnishing the supplies or services in the Schedule will be received at the place specified in Item 8, or if handcarried, in the depository located in [Block 8] *But see page 11 until 4:30 pm *(Hour)* local time 01/21/1999 *(Date)*

CAUTION -- LATE Submissions, Modifications, and Withdrawals: See Section L. Provision No. 52.214-7 or 52.215-10. All offers are subject to all terms and conditions contained in this solicitation.

10. FOR INFORMATION CALL:	A. NAME	B. TELEPHONE *(NO COLLECT CALLS)* AREA CODE	NUMBER	EXT.	C. E-MAIL ADDRESS
▶	William M. Stevens	301	435-0345	NA	ws69s@nih.gov

11. TABLE OF CONTENTS

(✓)	SEC.	PART I -- THE SCHEDULE		(✓)	SEC.	PART II -- CONTRACT CLAUSES	
✓	A	SOLICITATION/CONTRACT FORM	1	✓	I	CONTRACT CLAUSES	6-7
✓	B	SUPPLIES OR SERVICES AND PRICES/COSTS	2			PART III -- LIST OF DOCUMENTS, EXHIBITS AND OTHER ATTACH.	
✓	C	DESCRIPTION/SPECS./WORK STATEMENT	2-4	✓	J	LIST OF ATTACHMENTS	7
✓	D	PACKAGING AND MARKING	4			PART IV -- REPRESENTATIONS AND INSTRUCTIONS	
✓	E	INSPECTION AND ACCEPTANCE	4-5	✓	K	REPRESENTATIONS, CERTIFICATIONS AND OTHER STATEMENTS OF OFFERORS	7
✓	F	DELIVERIES OR PERFORMANCE	5-6				
✓	G	CONTRACT ADMINISTRATION DATA	6	✓	L	INSTRS., CONDS., AND NOTICES TO OFFERORS	7-32
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OFFER *(Must be fully completed by offeror)*

NOTE: Item 12 does not apply if the solicitation includes the provisions at 52.214-16, Minimum Bid Acceptance Period

12. In compliance with the above, the undersigned agrees, if this offer is accepted within _____ calendar days *(60 calendar days unless a different period is inserted by the offeror)* from the date for receipt of offers specified above, to furnish any or all items upon which prices are offered at the price set opposite each item, delivered at the designated point(s), within the time specified in the schedule.

13. DISCOUNT FOR PROMPT PAYMENT *(See Section I, Clause No. 52.232-8* ▶	10 CALENDAR DAYS %	20 CALENDAR DAYS %	30 CALENDAR DAYS %	CALENDAR DAYS %

14. ACKNOWLEDGMENT OF AMENDMENTS *(The offeror acknowledges receipt of amend-ments to the SOLICITATION for offerors and related documents numbered and dated:)*	AMENDMENT NO.	DATE	AMENDMENT NO.	DATE

15A. NAME AND ADDRESS OF OFFEROR	CODE	FACILITY	16. NAME AND TITLE OF PERSON AUTHORIZED TO SIGN OFFER *(Type or print)*

15B. TELEPHONE NO. AREA CODE/NUMBER	EXT.	☐ 15C. CHECK IF REMITTANCE ADDRESS IS DIFFERENT FROM ABOVE -- ENTER SUCH ADDRESS IN SCHEDULE.	17. SIGNATURE	18. OFFER DATE

AWARD *(To be completed by Government)*

19. ACCEPTED AS TO ITEMS NUMBERED	20. AMOUNT	21. ACCOUNTING AND APPROPRIATION

22. AUTHORITY FOR USING OTHER THAN FULL AND OPEN COMPETITION:	23. SUBMIT INVOICES TO ADDRESS SHOWN IN *(4 copies unless otherwise specified)* ▶	ITEM
☐ 10 U.S.C. 2304(c) ( ) ☐ 41 U.S.C. 253(c) ( )		

24. ADMINISTERED BY *(If other than Item 7)* CODE	25. PAYMENT WILL BE MADE BY CODE

26. NAME OF CONTRACTING OFFICER *(Type or print)*	27. UNITED STATES OF AMERICA *(Signature of Contracting Officer)*	28. AWARD DATE

IMPORTANT -- Award will be made on this Form, or on Standard Form 26, or by other authorized official written notice.

SECTION B—SUPPLIES OR SERVICES AND PRICES/COSTS

ARTICLE B.1. BRIEF DESCRIPTION OF SUPPLIES OR SERVICES

The "SOCRATES" trial will assess the benefits and risks comparing three clinically employed strategies (two medical anti-ischemic strategies and early revascularization) with respect to long term morbidity and mortality. The requirements set forth herein are for the SOCRATES Clinical Network Center (CNC).

ARTICLE B.2. PRICES/COSTS

a. The contractor shall be paid by the Government in accordance with the following schedule in response to monthly invoices of actual quantities and amounts, only when all deliverables and functions are accepted.

Item	Description	Qty	Unit Price ($)	Total
1.	Randomization	600	$X	$X
2.	3 month follow-up	600	$X	$X
3.	6 month follow-up	600	$X	$X
4.	Annual follow-ups	3,000	$X	$X
5.	Semi-annual follow-ups:	2,400	$X	$X
			Total Funded Amount	$X

b. The prices set forth in this ARTICLE B.2. will cover the contract period Septmber 30, 1999 through September 30, 2006.

SECTION C—DESCRIPTION/SPECIFICATIONS/WORK STATEMENT

(For a complete description of the Background and History, Statement of Work, and explanations of initials and acronyms, including study design requirements and considerations, refer to Section III, Project Information, in Section L below.)

ARTICLE C.1. STATEMENT OF WORK

Independently, and not as an agent of the Government, the contractor shall furnish all the necessary services, qualified personnel, material, equipment, and facilities not otherwise provided by the Government, as needed to perform of the work below. All proposed protocol activities are subject to change in finalizing the protocol. The SOCRATES trial shall be conducted in four phases: Protocol Finalization and Implementation, Recruitment, Follow-up, and Close-out and Analysis Phase. The proposed timetable is shown below. The following is a list of key activities the contractor for the Clinical Network Center (CNC) for SOCRATES shall:

1. Have a proposal for finalizing the step treatment drug regimens for the anti-ischemic medical strategies and for general medical treatment and aggressive risk factor management. This plan should anticipate a collaboration with other CNCs, the CDCC and other central units, and the Program Office in finalizing the protocol and manual of operations.

2. Have a plan for communication system within the CNC, including availability of access to Internet transmission. This plan should include means of assisting the CDCC in facilitating data gathering links between the CNC and central units (CDCC, core labs).

3. Have IRB clearance/assurances for all participating units within the network.

4. Have a plan for assisting the CDCC in training staff within the CNC in uniform protocol implementation, standardization of protocol-directed procedures and data collection. It is anticipated that the data will be transmitted from individual clinical units/clinical investigators within the CNC directly to the central (CDCC, core laboratories) units. The plan should also include a close collaboration with the CDCC in correcting problems with missed, delayed, and erroneous data at the respective clinical unit sites within the CNC.

5. Have a plan documenting the ability to recruit a minimum of 600 patients for randomization into the three treatment strategies, according to the above outlined protocol. Criteria for selection of CNC shall at a minimum include evidence of adequate patient population, and evidence of institutional support. The recruitment plan shall include plans for recruitment of women and minorities (African Americans, Hispanic, Native American, Asian), for evaluating and correcting recruitment problems, such as selection criteria of new sites and the appropriate follow-up of patients enrolled from sites that have ceased recruitment. The plan will also address means for assuring timely recruitment and high performance throughout the study duration, including conducting routine (e.g., yearly) and other site visits within the network, as needed. It is also anticipated that the CDCC will conduct one site visit per year to each CNC to assure protocol compliance and quality control measures.

6. Have a plan for accumulating and maintaining appropriate data files and maintain appropriate confidentiality and security of these files at the respective clinical unit sites.

7. Have a plan for assuring a high clinical performance for all clinical units enrolling and following patients within the CNC.

8. Have plans for performing the measurements in all patients, as outlined in the draft protocol (See Section III, Project Information, in Section L below).

9. Have a plan for coordination, arrangement, participation in, and provision of any information necessary for regular clinical investigator meetings within the CNC, including a preparation and distribution of minutes of each meeting and any other correspondence necessary to the participants, the CDCC and the Program Office, in a timely manner. Have a plan for selection of experts from within the CNC to represent and to attend the Steering Committee meetings (approximately twice a year) and other appropriate study activities.

10. Have a plan for assisting the CDCC in capturing major adverse effects in timely fashion to maximize patient safety and for prompt reporting of major adverse events from the appropriate clinical unit, through the CNC leadership, to the Program Office and the CDCC, according to the manual of operations and the protocol.

11. Participate in preparing data for publications in collaboration with other study investigators and the NHLBI Program Office.

12. Provide a concise final report which will serve as a technical reference document, describing all of the phase activities (2 copies), with the document in a format available for Internet transmission.

The trial shall be conducted in the following four phases:

Phase I Protocol Finalization and Implementation (6 months): Functions # 1-5 will be accomplished.

Phase II Recruitment (24 months): Perform functions # 5-10.

Phase III Follow-up (48 months): Perform functions similar to Phase II, except for enrollment.

Phase IV Close Out and Analyses (6 months): Perform functions # 11-12.

The Statement of Work, and the Background and History in Section III, Project Information, in Section L below, and the resultant Protocol and Manual of Operations shall be incorporated herein and considered a part of the Statement of Work.

ARTICLE C.2. REPORTING REQUIREMENTS

In addition to those reports required by the other terms of this contract, the Contractor shall prepare and submit the following reports in the manner stated below and in accordance with ARTICLE F.1. DELIVERIES of this contract:

(1) Data on a minimum of 600 patients shall be delivered to the CDCC. Laboratory and genetic specimens shall be delivered to the CDCC or the designated core laboratory.

(2) Monthly or Quarterly Financial Status Reports (Monthly Invoice or NIH 2706)

(3) Abstracts and manuscripts proposed for publication, in advance for NHLBI approval.

(4) An annual Technical Progress report shall be brief focusing on major changes and issues not previously reported, and will also include reports related to quality monitoring of the units within the CNC. Reports should not repeat written material distributed to the Steering Committee. Instead, the Contractor shall report on administrative matters, staffing changes, current staff (name, position and level of effort), and any problems, occurring or anticipated, related to its contract responsibilities, on solutions to the problems, and on general progress in each major activity. The first report shall be due within 30 days of the completion of the performance year. Thereafter, reports shall be due on or before the thirty-first calendar day following each year of performance, except that the annual report will not be required for the final year of the contract when the final technical progress report is due.

(5) A final technical report is to include a summation of the work performed for the entire contract period of performance. This report shall be brief describing the phase activities achieved. The Final Report shall be submitted on or before the last day of the contract performance period in accordance with ARTICLE F.1, DELIVERIES, of this contract.

(6) Summary of Salient Results. The contractor shall submit with the Final Report a summary (not to exceed 200 words) of salient results achieved during the performance of the contract.

SECTION D—PACKAGING, MARKING, AND SHIPPING

The Contractor shall guarantee that all required materials, such as laboratory samples, shall be delivered in immediately usable and acceptable condition.

ARTICLE E.1. INSPECTION AND ACCEPTANCE

a. The Contracting Officer or the duly authorized representative will perform inspection and acceptance of materials and services to be provided.

b. For the purpose of this ARTICLE, the Project Officer is the authorized representative of the Contracting Officer.

c. Inspection and acceptance will be performed at the National Heart, Lung, and Blood Institute, Two Rockledge Centre, 6701 Rockledge Drive, MSC 7940 (Project Office) and MSC 7902 (Contracts Office), Bethesda, Maryland 20892. Acceptance may be presumed unless otherwise indicated in writing by the Contracting Officer or the duly authorized representative within forty-five (45) days of receipt. The inspection and/or acceptance may be also performed at the Contractor's site.

d. This contract incorporates the following clause by reference, with the same force and effect as if it were given in full text. Upon request, the Contracting Officer will make its full text available.

FAR Clause No 52.246-8, INSPECTION OF RESEARCH AND DEVELOPMENT - COST REIMBURSEMENT (APRIL 1984)

SECTION F—DELIVERIES OR PERFORMANCE

ARTICLE F.1. PERIOD OF PERFORMANCE

The period of performance of the services described in this contract shall be from Septmber 30, 1999 through September 30, 2006, as follows:

Phase	PERIOD
Protocol implementation	September 30, 1999 through March 31, 2000
Recruitment	April 1, 2000 through March 31, 2002
Follow-up	April 1, 2002 through March 31, 2006
Analysis & Publication	April 1, 2006 through September 30, 2006

ARTICLE F.2. DELIVERABLES

a. Satisfactory performance of this contract shall be deemed to occur upon completion of the services described in ARTICLE C.1. and upon delivery and acceptance by the Contracting Officer, or the duly authorized representative, of the following items in accordance with the stated delivery schedule:

Item	Description	Delivered to:	Delivery Schedule
a.	Data on 600 Patients, laboratory specimens and genetic specimens	As directed by the Protocol and Manual of Operations	As Recruited
b.	Financial Status Report	Contracting Officer	Monthly or Quarterly
c.	Abstracts and manuscripts	Project Officer	Prior to publication
d.	Annual Progress Report	Project Officer and Contracting Officer	Annually
e.	Final Report, hard and electronic copies	Project Officer and Contracting Officer	September 30, 2006
f.	Summary of Salient Results	Project Officer and Contracting Officer	September 30, 2006

Copies of reports shall be sent to the following addresses:

Addressee	Item	Quantity
Project Officer Heart Research Program, DHVD, NHLBI 6701 ROCKLEDGE DR MSC 7940 BETHESDA MD 20892-7940	(d) (c) (e,f)	1 3 As directed
Contracting Officer Contracts Operations Branch, DEA, NHLBI 6701 ROCKLEDGE DR MSC 7902 BETHESDA MD 20892-7902	(b,d,e,f)	3
Coordinating Center To be Determined	(a)	As directed

SECTION G—CONTRACT ADMINISTRATION DATA

(NOTE: See "Sample Contract Format- General" for potential Section G. Articles which will be accessed at the following web site: http://www4.od.nih.gov/ocm/contracts/rfps/sampkt.htm.)

SECTION H—SPECIAL CONTRACT REQUIREMENTS

(NOTE: See "Sample Contract Format- General" for potential Section H. Articles which will be accessed at the following web site: http://www4.od.nih.gov/ocm/contracts/rfps/sampkt.htm.)

PART II, CONTRACT CLAUSES

(NOTE: The following section for General Clause Listings can be accessed at the following web site: http://amb.nci.nih.gov/Clauses/Clauses.html.)

SECTION I—CONTRACT CLAUSES

ARTICLE I.1. GENERAL CLAUSES FOR A NEGOTIATED COST REIMBURSEMENT RESEARCH AND DEVELOPMENT CONTRACT [Educational, Nonprofit, or other depending on organizational status of offeror; select appropriate article]—CLAUSES INCORPORATED BY REFERENCE (FEBRUARY 1998)

This contract incorporates the referenced clauses with the same force and effect as if they were given in full text. Upon request, the Contracting Officer will make their full text available [FAR 52.252-2 (JUN 1988), Alternate I (JUN 1988)].

ARTICLE I.2. AUTHORIZED SUBSTITUTIONS OF CLAUSES

The following clause(s) are part of this contract:

a. FAR clause 52.215-26, Alternate I (APRIL 1991) is added to FAR clause 52.215-26, INTEGRITY OF UNIT PRICES (APRIL 1991)

b. FAR Clause no. 52.215-27, TERMINATION OF DEFINED BENEFIT PENSION PLANS (MARCH 1996), is deleted in its entirety.

ARTICLE I.3. ADDITIONAL CONTRACT CLAUSES

This contract incorporates the following by reference, with the same force and effect as if they were given in full text. Upon request, the Contracting Officer will make their full text available.

a. FEDERAL ACQUISITION REGULATION (FAR) (48 CFR CHAPTER 1) CLAUSES:

(1) FAR 52.203-12, Limitation on Payments to Influence Certain Federal Transactions (JANUARY 1990)

(2) FAR 52.219-14, Limitation on Subcontracting (JANUARY 1991)

(3) FAR 52.227-14, Rights in Data—General (JUNE 1987)

b. DEPARTMENT OF HEALTH AND HUMAN SERVICES ACQUISITION REGULATION/ PUBLIC HEALTH SERVICE ACQUISITION REGULATION (HHSAR) (PHSAR) (48 CFR CHAPTER 3) CLAUSES:

< None >

c. NATIONAL INSTITUTES OF HEALTH (NIH) RESEARCH CONTRACTING (RC) CLAUSES:

The following clause is attached and will be made a part of any contract resulting from this RFP.

NIH(RC)-7, Procurement of Certain Equipment (APRIL 1984) (OMB Bulletin 81-16)

PART III—LIST OF DOCUMENTS, EXHIBITS, AND OTHER ATTACHMENTS

SECTION J—LIST OF ATTACHMENTS

See listing of RFP and Contract attachments in Section L below.

PART IV—REPRESENTATIONS AND INSTRUCTIONS

SECTION K—REPRESENTATIONS AND CERTIFICATIONS

The Representations, Certifications, and Other Statements of Offerors or Quoters (Negotiated) for this RFP are available at **http://www4.od.nih.gov/ocm/contracts/rfps/REPCERT.htm**. Please see also the instructions for the attached form in the listing of RFP and Contract attachments in Section L below.

SECTION L—INSTRUCTIONS, CONDITIONS, AND NOTICES TO OFFERORS

THIS SECTION OF THE RFP CONSISTS OF THE FOLLOWING SECTIONS:

I. Specific RFP Instructions and Provisions,

II. Applicable RFP References, and

III. Project Information

I. SPECIFIC RFP INSTRUCTIONS AND PROVISIONS

NOTICE TO OFFERORS: This section contains proposal instructions and information which are specifically related to this acquisition. The information provided below is only a portion of the instructions and notices required for the submission of a proposal. References to additional, more general, information and forms regarding proposal preparation are contained under Section III. Applicable RFP References.

The following specific RFP instructions and provisions apply to this Request For Proposal:

A. Proposal Intent Response Sheet (submit prior to proposal submission—by December 21, 1998)

B. GOVERNMENT NOTICE FOR HANDLING PROPOSALS

C. Packaging and Delivery of Proposal

D. SIC Code and Small Business Size Standard

E. Number and Type of Award(s)

F. Estimate of Effort

G. Service of Protest

H. Technical Proposal Table of Contents

I. Page Limits

J. Other Provisions

A. PROPOSAL INTENT RESPONSE SHEET

RFP No. NHLBI-HC-99-15

TITLE OF RFP:Study of Coronary Revascularization And Therapeutics Evaluations (SOCRATES)

FURNISH THE INFORMATION REQUESTED BELOW AND RETURN THIS PAGE BY **DECEMBER 21, 1998**. YOUR EXPRESSION OF INTENT IS NOT BINDING BUT WILL ASSIST US IN PLANNING FOR PROPOSAL EVALUATION.

We urge potential offerors to consider sufficiently whether they can adequately address Technical Evaluation Criterion #1: Adequacy of documentation showing an ability to recruit a total of 600 patients. Note that this criterion is given 30 out of the 100 points of the total assessment of technical merit of the proposal. Only offerors that can fully address this criterion can expect to be competitive for this award.

If you decide to submit a proposal, it is IMPORTANT that you FAX a letter of intent with the complete list of all key personnel that you plan to collaborate with in this study that are not part of your institution.

I INTEND TO SUBMIT A PROPOSAL

COMPANY/INSTITUTION NAME:

ADDRESS:

PROJECT DIRECTOR'S NAME:

TITLE:

TELEPHONE NUMBER:

NAMES OF COLLABORATING INSTITUTIONS AND INVESTIGATORS
(include Subcontractors and Consultants):

RETURN TO:

Review Branch
NIH, NHLBI
6701 ROCKLEDGE DR MSC 7924
BETHESDA MD 20892-7924

Attention: Dr. James Scheirer

or FAX TO: Dr. James Scheirer at (301) 480-3541

B. NOTE: This Notice is for the Technical Evaluation Review Group who will be reviewing the proposals submitted in response to this RFP. THE OFFEROR SHALL PLACE A COPY OF THIS NOTICE BEHIND THE TITLE PAGE OF EACH COPY OF THE TECHNICAL PROPOSAL.

GOVERNMENT NOTICE FOR HANDLING PROPOSALS

This proposal shall be used and disclosed for evaluation purposes only, and a copy of this Government notice shall be applied to any reproduction or abstract thereof. Any authorized restrictive notices which the submitter places on this proposal shall be strictly complied with. Disclosure of this proposal outside the Government for evaluation purposes shall be made only to the extent authorized by, and in accordance with, the procedures in HHSAR paragraph 315.608-72.

(f) If authorized in agency implementing regulations, agencies may release proposals outside the Government for evaluation, consistent with the following:

(1) Decisions to release proposals outside the Government for evaluation purposes shall be made by the agency head or designee;

(2) Written agreement must be obtained from the evaluator that the information (data) contained in the proposal will be used only for evaluation purposes and will not be further disclosed;

(3) Any authorized restrictive legends placed on the proposal by the prospective Contractor or subcontractor or by the Government shall be applied to any reproduction or abstracted information made by the evaluator;

(4) Upon completing the evaluation, all copies of the proposal, as well as any abstracts thereof, shall be returned to the Government office which initially furnished them for evaluation; and

(5) All determinations to release the proposal outside the Government take into consideration requirements for avoiding organizational conflicts of interest and the competitive relationship, if any, between the prospective Contractor or subcontractor and the prospective outside evaluator.

(g) The submitter of any proposal shall be provided notice adequate to afford an opportunity to take appropriate action before release of any information (data) contained therein pursuant to a request under the Freedom of Information Act (5 U.S.C. 552); and, time permitting, the submitter should be consulted to obtain assistance in determining the eligibility of the information (data) in question as an exemption under the Act. (See also Subpart 24.2, Freedom of Information Act.)

.

C. PACKAGING AND DELIVERY OF THE PROPOSAL

Your proposal shall be organized as specified in the "Standard RFP Instructions and Provisions." Shipment and marking shall be as follows:

EXTERNAL PACKAGE MARKING
In addition to the address cited below, mark each package as follows:

"RFP NO. NHLBI-HC-98-32
TO BE OPENED BY AUTHORIZED GOVERNMENT PERSONNEL ONLY"

The numbers of copies required of each part of your proposal are:
TECHNICAL PROPOSAL: ORIGINAL* AND Twenty-five (25) COPIES

BUSINESS PROPOSAL: ORIGINAL* AND Six (6) COPIES Plus
One Attached Electronic Business Proposal Spread Sheet (EXCEL Spread Sheet on disk)

DELIVER PROPOSAL TO:

Review Branch, Division of Extramural Affairs
National Heart, Lung, and Blood Institute, NIH
Rockledge Building, Room 7091
6701 ROCKLEDGE DR MSC 7924
BETHESDA MD 20892-7924

*THE ORIGINAL PROPOSAL MUST BE READILY ACCESSIBLE FOR DATE STAMPING. IN ADDITION, EVERY SEPARATELY BOUND VOLUME **MUST** CONTAIN THE ORGANIZATION'S NAME, ADDRESS, AND RFP NUMBER

D. SIC CODE AND SMALL BUSINESS SIZE STANDARD

NOTE: The following information is to be used by the offeror in preparing its Representations and Certifications, specifically in completing the provisions entitled, SMALL BUSINESS PROGRAM REPRESENTATIONS, FAR 52.219-1:

The standard industrial classification (SIC) code for this acquisition is 8731.

The small business size standard is 500 employees.

THIS REQUIREMENT IS **NOT** SET-ASIDE FOR SMALL BUSINESS.

E. NUMBER AND TYPE OF AWARD(S)

It is anticipated that TEN awards will be made as incrementally funded cost-reimbursement type contracts with a fixed fee component to Clinical Network Center (CNC) .

A capitation-rate will be used for the recruitment and follow up portions of the trial. Payment shall be reimbursed upon verification by the Clinical Data Coordinating Center that the data/information was received in an accurate and timely manner. For details of the payment plan, see ARTICLE B.2. Prices.

F. Level of Effort. The Government considers that the personnel and estimated levels of effort listed below will be required for successful completion of the study. Effort is shown as a percentage of FTE (full time equivalent) labor. **The effort is listed below as information only and is not to be considered restrictive for proposal purposes.**

It is expected that a completion, cost-reimbursement type combined with capitation-rate* type contract will be awarded as a result of this RFP. To assist you in the preparation of your proposal, the Government considers the effort to be approximately 1.3 FTE for phase 1. This information below is furnished for the offeror's information only and is not to be considered restrictive for proposal purposes.

Labor Category	Year 1	Years 2 - 7
Principal Investigator	10%	Costs
Co-Principal Investigator	20%	Based on
CNC Coordinator	50%	Capitation
Secretary/Clerical/Admin.	50%	Rates
Total:	130%	

* The NHLBI anticipants reimbursement of the following capitation-rates:

Item	Description	Unit Price ($)
1.	Randomization	$1,500
2.	3 month follow-up	$100
3.	6 month follow-up	$100
4.	Annual follow-ups	$175
5.	Semi-annual follow-ups:	$100

G. SERVICE OF PROTEST

In accordance with FAR 52.233-2 SERVICE OF PROTEST (NOV 1988):

(a) Protests, as defined in Section 33.101 of the Federal Acquisition Regulation, that are filed directly with an agency, and copies of any protests that are filed with the General accounting Office (GAO) shall be served on the Contracting Officer (addressed as follows) by obtaining written and dated acknowledgment of receipt from:

Mr. William M. Stevens

Address:
National Institutes of Health
National Heart, Lung, and Blood Institute
Contracts Operations Branch
Rockledge 2, Room 6118
6701 ROCKLEDGE DR MSC 7902
BETHESDA MD 20892-7902

The copy of any protest shall be received in the office designated above within one day of filing a protest with GAO.

H. TECHNICAL PROPOSAL TABLE OF CONTENTS

Please number each page of text. Type density and size must be 10-12 points. If constant spacing is used, there should be no more than 15 cpi, whereas proportional spacing should provide an average of no more than 15 cpi. There must be no more than six lines of text within a vertical inch.

The technical proposal should be organized as follows:

1. **TECHNICAL PROPOSAL COVER SHEET** (Form is located in the Streamlined RFP References under "http://www4.od.nih.gov/ocm/contracts/rfps/forms1.htm" Page 1

2. **TECHNICAL PROPOSAL TABLE OF CONTENTS** . . . . . Page 2

3. **ABSTRACT** . . . . . Page 3
State the proposal's broad, long-term objectives and specific aims. Briefly and concisely describe the research design and methods for achieving these goals. DO NOT EXCEED one page in providing the abstract. Identify the RFP Number, Institution and Principal Investigator on the abstract.

4. **TECHNICAL PLAN** (no more than 50 PAGES single-spaced)
Refer to Technical Proposal Instructions located in the Standard RFP Instructions and Provisions under Streamlined RFP References for more detail.

   A. PERSONNEL

      (1) List of all prime contractor Personnel in the project, plus only Key Personnel from other organizations, by name, title, department and organization . . . . . Page #

      Please list all other Personnel in the project under Subcontractors, Consultants/Collaborators, by name, title, department and organization in the Business Proposal.

      PROVIDE NARRATIVE FOR:

      (2) Principal Investigator/Project Director . . . . . Page #

      (3) Other Investigators . . . . . Page #

      (4) Additional Personnel . . . . . Page #
      [NOTE: For personnel, include a two-page biosketch under APPENDICES below.]

   B. WORK STATEMENT

      (1) Objectives . . . . . Page #

      (2) Approach . . . . . Page #

      (3) Methods . . . . . Page #

      (4) Schedule . . . . . Page #

   C. FACILITIES, EQUIPMENT AND OTHER RESOURCES . . . . . Page #

      List/describe all facilities, equipment and other resources available for this project.

   D. OTHER CONSIDERATIONS . . . . . Page #
   (Use specifically titled subparagraphs, as applicable.)

5. **OTHER SUPPORT** . . . . . Page #

Complete the Form "Summary of Current and Proposed Activities." All key personnel must be listed on this form. The form is located in the Streamlined RFP References under "FORMS, FORMATS, & ATTACHMENTS."

6. TECHNICAL PROPOSAL COST INFORMATION . . . . . Page #

(Form located in the Streamlined RFP References under "FORMS, FORMATS, & ATTACHMENTS.")

7. LITERATURE CITED . . . . . Page #

8. APPENDICES . . . . . Page #

Total number of appendices shall not exceed 100 pages single-spaced. List each Appendix and identify the number of pages for each one. Appendices must be clear and legible, and easily located. Include biosketches here.

I. Page Limits

The offerors shall limit their responses to 150 pages. The technical approach must be limited to 50 pages. The APPENDICES of the proposal must be limited to 100 pages.

The cover sheet, abstract, table of contents, resources and facilities, other support, and literature cited are NOT "technical approach" and do not count against the 50 page limit. Consequently, the "technical approach" comprises item 4 of the "TECHNICAL PROPOSAL TABLE OF CONTENTS," exclusive of all subheadings except item a., Personnel. Note, however, that resumés or c.v.s or other documentation of individuals' capabilities should be provided in the appendices.

J. OTHER PROVISIONS

1. GOVERNMENT FURNISHED FACILITIES AND EQUIPMENT—None.

2. POTENTIAL AWARD WITHOUT DISCUSSIONS—The Government reserves the right to award a contract without discussions if the Contracting Officer determines that the initial prices are fair and reasonable and that discussions are not necessary. If award will be made without conducting discussions, offerors may be given the opportunity to clarify certain aspects of their proposal (e.g., the relevance of an offeror's past performance information and adverse past performance information to which the offeror has not previously had an opportunity to respond) or to resolve minor or clerical errors.

3. COST/PRICING INFORMATION—The offeror's business proposal shall include the basic cost/pricing information specified in the Standard RFP Instructions and Provisions, under the Streamlined RFP References Directory referenced in this RFP. Please include information to substantiate the proposed costs or prices. including payroll documentation, vendor quotes, invoice prices, and/or any other information relevant to aid the Government in evaluating the reasonableness of the price or to determine cost realism. Before award, submission and certification of cost or pricing data may be required. Please submit a computer disc with the cost proposal in Excel 5.0 (or 97) format. For your convenience, a standard cost proposal format in Excel is available at the bottom of the page at http://www4.od.nih.gov/ocm/contracts/rfps/buscost.htm.

4. PUBLICATION AND PUBLICITY (It is anticipated that this clause will appear in the contract.)

   The contractor shall acknowledge the support of the National Institutes of Health whenever publicizing the work under this contract in any media by including an acknowledgment substantially as follows:

   > This project has been funded in whole or in part with Federal funds from the National Heart, Lung and Blood Institute, National Institutes of Health, under Contract No. . . .

5. HHSAR 352.270-6 PUBLICATION AND PUBLICITY (JULY 1991) (It is anticipated that this clause will appear in the contract.)

   > Unless otherwise specified in this contract, the Contractor is encouraged to publish, and make available through accepted channels, the results of its work under this contract. A copy of each article submitted by the Contractor for publication shall be promptly sent to the Project Officer. The Contractor shall also inform the Project Officer when the article or other publication is published, and furnish a copy of it as finally published.

II. APPLICABLE RFP REFERENCES

This section identifies the items located in the Streamlined RFP References that are applicable to this Request For Proposal (RFP).

A. The entire file entitled "STANDARD RFP INSTRUCTIONS AND PROVISIONS" is applicable to this RFP, except as modified by the inclusion of items from the "OPTIONAL RFP INSTRUCTIONS AND PROVISIONS" below.

B. The following items are applicable from the file entitled "OPTIONAL RFP INSTRUCTIONS AND PROVISIONS." The full text of the provisions is available in the file available at http://www4.od.nih.gov/ocm/contracts/rfps/INSTOPT.htm.

   List of provisions which apply to this specific RFP:

   E. Late Proposals, Modifications of Proposals, and Withdrawals of Proposals

   N. Facilities Capital Cost of Money

   Q. ADP Systems Security

C. The following items are applicable to this specific RFP and are located in the file entitled "FORMS, FORMATS, AND ATTACHMENTS," under Streamlined RFP References:

SUBMIT WITH TECHNICAL PROPOSAL (with original and every copy of technical proposal)

1. Technical Proposal Cover Sheet
2. Summary of Current and Proposed Activities
3. Technical Proposal Cost Information

SUBMIT WITH BUSINESS PROPOSAL:

4. As the Business Proposal Cover Sheet, the Solicitation, Offer, and Award form SF-33, at the beginning of this document, specifically incorporating the Technical Proposal by reference.

5. Contract Pricing Proposal Cover Sheet, SF-1411, or equivalent, with every copy of business proposal.
6. Proposal Summary and Data record, NIH-2043, with every copy of business proposal.
7. Disclosure of Lobbying Activities, OMB SF-LLL, only one completed and signed original. This form is not required if there are no lobbying activities to disclose.
8. Filled out and signed contract proposal including the cover sheet form SF-33 and all subsequent pages. This includes quantities, unit prices, and totals within Article B.2.
9. Representations and Certifications, only one completed and signed original. (Attached at end of this document.)
10. One Attached Electronic Business Proposal Spread Sheet (EXCEL Spread Sheet on disk) available at http://www4.od.nih.gov/ocm/contracts/rfps/buscost.htm.

OTHER—TO BE SUBMITTED LATER:

11. Certificate of Current Cost or Pricing Data, NIH-1397, to be submitted with Final Proposal Revision, if required by the Contracting Officer.

ANTICIPATED TO BE INCLUDED AS CONTRACT ATTACHMENTS:

12. Invoice/Financing Requests Instructions for NIH Cost Reimbursement Type Contracts, NIH(RC)-2
13. Procurement of Certain Equipment, NIH(RC)-7
14. Privacy Act System of Records
15. Small, Small Disadvantaged and Women-Owned Small Business Subcontracting Plan

III. Project Information

Background and History

Coronary heart disease (CHD) is the leading cause of mortality and morbidity in the United States. The first clinical presentation of CHD can be angina, myocardial infarction (MI), or potentially fatal arrhythmia. It is estimated that 15% of all MIs are silent and 20 - 30% of sudden deaths have no history of angina. Nearly 600,000 patients each year are discharged alive from U.S. hospitals following MI, with 20-30% of these patients having ischemia, either asymptomatic or symptomatic, on predischarge exercise stress testing. Approximately 13 million Americans have chronic CHD, with potentially two-thirds of these having cardiac ischemia. Current projections indicate that the prevalence of chronic CHD increases continuously and will double between 1985 and 2010. Episodes of ischemia can be detected by various methods, such as AECG, stress testing, radionuclide angiography, and positron emission tomography. In patients with CHD, objective evidence of ischemia (on stress test or ambulatory AECG-monitoring), whether symptomatic or asymptomatic identifies individuals with an adverse prognosis [1].

The results of the older trials largely defined the relative places of medical therapy and coronary surgery for the era in which they were conducted. A number of significant changes in selection of patients for surgery, in surgical methods, and in medical therapies have occurred. New

pharmacologic and revascularization strategies are now available to relieve angina in patients with stable CHD. However, their effect on long-term functional status and survival has not been tested. Recently completed short-term trials suggest that coronary revascularization and medical suppression of ischemia could be beneficial in preventing future events. Therefore, for many patients uncertainty remains about optimal anti-ischemic strategy, such as revascularization vs. medical therapy.

Anti-Ischemic strategies: the role of drug therapies

Initially, the therapeutic options to control ischemia were limited. Nitroglycerin was the primary drug to relieve severe angina. With better understanding of the role that ischemia may play in future cardiovascular events and availability of new anti-ischemic drugs, medical strategies to control ischemia have expanded [2]. Beta blockers have been shown to reduce daily ischemia [3]. Benefits and risks of calcium channel antagonists anti-ischemic agents have been recently debated, with studies yielding conflicting results [4-6]. New generations of calcium channel antagonists with negative chronotropic effects and new beta adrenergic blockers have shown promising results in randomized studies, providing a link between reduction of ischemia, vasodilation and heart rate lowering and improved short term clinical outcome [7,8].

The short-term clinical outcomes were studied in recently conducted six medium sized randomized trials, in patients with stable CHD, using new and "old" anti-ischemic drugs. In the Atenolol Silent Ischemia Study (ASIST) 306 patients with objective evidence of ischemia were randomized to atenolol or placebo and followed for up to a year. The beta blocker significantly reduced the frequency and duration of daily ischemia. Event rates (MI, death, hospitalization for ischemia, or revascularization) were lower in atenolol arm compared to placebo [9]. The next 5 trials studied both beta blockers and calcium channel antagonists. In the Total Ischemic Burden European Trial (TIBET) 682 patients were randomized to atenolol, slow release nifedipine, or a combination of both and followed for 2 years[10]. In Angina Prognosis Study in Stockholm (APSIS) 809 patients were randomized to metoprolol or verapamil and followed for an average of 3.4 years [11]. In the Total Ischemic Burden Bisoprol Study (TIBBS) 520 patients were randomized to either bisoprol or slow release nifedipine for 8 weeks [12]. Neither of these studies comparing calcium channel blockers to beta blockers showed any significant difference in survival-free of MI, but the studies did not have statistical power to detect such differences. Both class agents reduced the number of ischemic episodes with beta blocker being more effective. Several studies showed a trend toward a lower rate of combined events (death, MI, hospitalization of ischemia or revascularization) with anti-ischemic therapy [13]. Therefore, the question of anti-ischemic therapy on long-term prognosis remains unanswered.

The ischemic hypothesis was also tested in the Asymptomatic Cardiac Ischemia Pilot (ACIP), a NHLBI-funded study. The ACIP was designed to determine the feasibility of both recruiting patients and implementing medical and revascularization anti-ischemic interventions, and to provide more reliable estimates of event rates in preparation for a definitive trial. At 10 centers, 558 patients with coronary disease amenable to revascularization, ischemia on stress tests, and at least one asymptomatic ischemic episode on AECG were randomized to either: 1) immediate revascularization of all important stenoses with either PTCA or CABG (selected by the patient's physician); 2) angina-guided therapy, using anti-ischemic drug regimens to relieve angina; or 3) ischemia-directed therapy, using anti-ischemic drug regimens to suppress both angina and AECG-documented ischemia. Randomization was stratified by center, presence or absence of angina, and previous CABG or no previous CABG. Therapy in the two medical arms was double-blinded and placebo controlled with regard to evidence for and treatment of AECG-documented ischemia. Within each medical arm, patients were randomized to one of the two protocol medication sequences, either atenolol followed by (long acting) nifedipine or (long acting) diltiazem followed by isosorbide dinitrate. The primary

outcome measure was elimination of ischemia on the AECG and absence of ischemic events at 12 weeks. Secondary outcomes included ECG exercise test responses and clinical events. Patients were followed for a minimum of 24 months. At 12 weeks, in the medical strategies, the 2 medical protocol combinations were similar in suppression of AECG ischemia. The greatest abolition of AECG ischemia was directly related to the greatest heart rate reduction [17].

Compliance with treatment strategies for the one-year trial was excellent. At one-year follow-up coronary revascularization was the best in suppressing ischemia and had the best clinical outcome. The mortality rate at 1 year was 4.4% in the angina-guided medical care group, 1.6% in the ischemia-directed group and 0% in the revascularization group; the rates for death or MI were 8.8%, 6.0%, and 2.6%, respectively. The frequency of MI, unstable angina, stroke and CHF was not significantly different among the three strategies [13-17]. A recently published two-year follow-up (one year beyond the trial) showed that the clinical outcomes continued to remain different among the three groups [18]. Clinical outcome rates for the ischemia-guided medical therapy were intermediate between the angina-guided arm and revascularization. The two-year total mortality was 6.6% in the angina-guided group, 4.4% in the ischemia-directed group, and 1.1% in the revascularization group ($p = 0.02$). The two-year rate of death or MI was 12.1%, 8.8% and 4.7% ($p = 0.04$), respectively. The two-year rate of death, MI, or recurrent cardiac hospitalization was 41.8%, 38.5%, and 23.1% ($p < 0.01$), respectively. However, the results are not as definitive as the p-values suggest. The 1.1% mortality over two years in the revascularization group was lower than generally expected in such patients. The titration scheme of the anti-ischemic medications over 12 weeks was too brief and limited its effectiveness. Risk factor control reflected common practice in the early '90s. In summary, the ACIP was a pilot study and not the full scale trial to address the issue of whether more intensive anti-ischemic medical therapy improves prognosis.

These studies confirmed previous observations that frequent episodes of transient ischemia is a marker for increased cardiac event rate, and reduction in ischemia may improve clinical outcomes. The available data show that beta blockers and calcium channel antagonists, with the exception of short acting nifedipine, are reasonable choices for reducing ischemia[13]. However, the question of survival benefit with anti-ischemic therapy remains to be answered.

Anti-Ischemic strategies: the role of revascularization

Beginning in the early 1970's, with popularization of revascularization a number of studies reported on the experience of CABG. There were three large, clinical randomized trials of CABG versus medical therapy which affected clinical practice. In the Veterans Administration Cooperative Study of Coronary Artery Bypass Surgery for stable angina, 686 male CHD patients with stable ischemia were followed for at least 11 years. An improved survival with CABG, noted at 7 years, was no longer present at 11 years [19,20]. The best survival was noted in a subgroup of patients with significant left main stenosis, 3-vessel disease and impaired LV function, or high clinical risk. In the European Coronary Surgery Study, 767 men with mild to moderate angina and at least 2-vessel CHD were followed up to 12 years. The survival benefit with CABG was noted at 5 years. As with the above VA study, the survival benefit with CABG began to decrease after 5 years, due to higher mortality in the surgical group [21,22], and the best benefit was noted in a subgroup of patients at high risk. In the Coronary Artery Surgery Study (CASS), 780 patients with mild angina (Canadian Cardiovascular Society Class (CCSC) I or II) or asymptomatic after MI were followed for at least 15 years. There was no significant difference in survival between the medically and surgically assigned groups [23,24]. However, a subgroup of patients with 3-vessel disease and an EF < 50% had a significantly better survival with CABG [25,26]. At the end of 12 years of follow-up, a substantial number of patients required CABG: 46% of those with 2-vessel disease, and 60% of those with 3-vessel disease.

These three trials became landmark studies influencing contemporary therapy. Despite enrolling different patient populations, all three trials showed improved survival of high-risk patients with CABG. Due to the available technology, higher risk patients, such as those aged > 65, those with more severe angina, and those with evidence of severe LV dysfunction were excluded, all of whom represent a significant proportion of the population of CHD patients currently managed. A recent meta-analysis of the data from the three cited trials and from other smaller randomized trials, comparing the long-term mortality of medical vs. routine (early) CABG strategy, showed improved survival in high-risk patients [27]. Interestingly, the incidence of MI, LV function, or the likelihood of return to employment was not improved with CABG. A number of major advances have been made since these trials took place. Internal mammary artery grafts for CABG, cardioplegia, limitation of operative wound to minimize or avoid sternal injury, beta blockers, lipid lowering drugs, antiplatelet agents, and angiotensin-converting enzyme (ACE) inhibitors are among advances now routinely used, each documented to improve clinical outcomes.

During the time that the above trials comparing CABG to medical therapy were ongoing, PTCA was introduced into clinical practice and used in very selected patients. However, its use rapidly expanded to a wide range of patients. In 1980, fewer than 6,000 PTCAs were performed, with 131,000 done in 1986, to more than 410,000 done in 1996[28.] The NHLBI-funded PTCA registries documented the relative safety and experience with the new catheter-based technologies [29]. It is used to relieve angina and/or ischemia in patients with severe CHD. It has been also used in asymptomatic CHD patients even without evidence of myocardial ischemia. Its broader use may reflect a number of anticipated, but not documented benefits in hope of preventing future events. However, the data from randomized trials or prospective observational studies comparing PTCA to medical therapy to support such applications are lacking. These concerns are reflected in the American College of Cardiology and American Heart Association (ACC/AHA) Joint Task Force Guidelines for PTCA [30] which recommend PTCA for certain subgroups of asymptomatic or mildly symptomatic CHD (CCS Class I) patients with 1-vessel or multi-vessel disease: (a) 1-vessel CHD with a "large area" of ischemic myocardium subtending a significant (≥ 50% diameter reduction) coronary stenosis (ACC/AHA Class I = definite indication for PTCA) or a "moderate area" of ischemia (ACC/AHA Class II = probable but uncertain indication); and (b) multi-vessel CHD with a "large ischemic area" (ACC/AHA Class I) or "moderate ischemic area" (ACC/AHA Class II indications).

In comparison to CABG, there are few randomized trials comparing (early) revascularization with PTCA to medical therapy. In the Angioplasty Compared to Medicine Evaluation (ACME) trial, 212 patients with stable angina or a recent MI, and significant stenosis of one major coronary artery, and a positive exercise test were followed for at least 6 months [31]. By 6 months, both strategies significantly improved exercise capacity, with better improvement and less angina in the PTCA group, but the group also ended up with a higher rate of CABG. The results suggested that PTCA improved symptom and exercise performance over medical therapy which was best in those with 1-vessel disease; however, the number of patients with 2-vessel disease was small [31]. In the recently completed second Randomized Intervention Treatment of Angina (RITA 2) study, 1,018 patients with stable CHD were followed for > 3 years. The PTCA strategy was associated with greater symptomatic improvement, but it did not alter mortality, and was associated with increased MI rates[32]. Criticisms raised included the fact that the patient population was also relatively low risk, the PTCA deployed few new techniques (few stents), and the medical therapy, especially lipid lowering, was not sufficiently intensive. One of the interpretations of the results from both ACME and RITA 2 results may be that for stable patients PTCA could be safely deferred while medical therapy was tried first.

As previously discussed, the ACIP studied revascularization as well as medical anti-ischemic strategies. The mode of revascularization was nearly equally divided between PTCA and CABG. As indicated above, 2- year follow-up showed that the clinical outcomes were best with revascularization strategy [18].

Lastly, there has been discussion about potential anti-ischemic effects of HMG-CoA reductase agents. The issue whether intense lipid lowering with a statin, atorvostatin, can significantly delay or obviate the need for catheter-based revascularization is being studied in the ongoing Aggressive Lipid Lowering With Atorvostatin Versus Revascularization Treatment (AVERT) trial. The cohort of 341 patients with a significant CAD, asymptomatic or angina (CCSS class < 2), was randomized to PTCA accompanied by usual care or aggressive lipid lowering with atorvostatin, and will be followed for 18 months. The study is expected to be completed in June 1998 [33].

Medical strategies: the role of contemporary risk factor management

Concurrent with the rapid evolution and expansion of PTCA and CABG use, there have been equally dramatic changes in medical therapy. A number of studies have shown that appropriate therapy halt the progression of CHD and prevent clinical events in CHD [34-39]. Aspirin lowers cardiac mortality and MI in both men and women with stable CHD [41, 42], beta-blockers improve survival after myocardial infarction, and ACE inhibition improves survival in patients with LV dysfunction after acute MI [43-44].

Lipid lowering, primarily using the HMG-CoA reductase inhibitors, significantly decreases coronary events, including the need for myocardial revascularization procedures, without any evidence of increased non-cardiac mortality in statin-treated patients and improves survival in both primary and secondary prevention trials [45-46]. The Cholesterol and Recurrent Events Trial (CARE) studied 4,159 CHD patients randomized to pravastatin or placebo over 5 years. Pravastatin significantly reduced fatal coronary events or non-fatal MI by 24%, with no difference in total mortality [47]. In the Regression Growth Evaluation Statin Study (REGRESS) 69 patients with angiographic CHD were randomized into pravastatin or placebo and followed for 2 years with myocardial perfusion studies. Pravastatin improved myocardial perfusion, in the absence of angiographic improvement, and also decreased transient myocardial ischemia. The discrepancy between perfusion improvement and lack of angiographic improvement was attributed to improved endothelial function with pravastatin [48-49].

Thus, our past view of medical therapy and myocardial revascularization needs to be reevaluated. Recent data suggest strongly that intensive medical therapy (e.g., aspirin; anti-ischemic therapy with beta-blockers and/or calcium antagonists; lipid lowering therapy; and ACE inhibitors) may not only ameliorate angina, but may decrease mortality and nonfatal MI in patients with stable CHD. Such therapeutic developments, in the context of parallel advances in coronary revascularization procedures, offer hope that the early use of revascularization coupled with proven secondary prevention interventions may optimize the management of CHD patients and provide long-term clinical benefits.

Summary

In summary, ischemia confers a higher risk for future events, and plays an important role in determining a type of therapy for many of these patients. The results of the older trials largely defined the relative places of medical therapy and revascularization, primarily by coronary surgery for the era in which they were conducted. Substantial changes in medical therapies and revascularization methods, and in patients selected for these therapies, have made significant impact on patients' immediate outcome and long term prognoses. Aggressive risk factor modification has been shown to lower mortality and morbidity in patients with CHD. With a number of pharmacologic and mechanical approaches able to suppress ischemia, new therapeutic concepts have

emerged based on the belief that alleviation of ischemia, whether symptomatic or asymptomatic, will lower long-term morbidity and mortality. Recently completed trials suggest that mechanical revascularization and suppression of ischemia could be beneficial in preventing future events.

Experience from the ACIP and ACME studies, the two studies most relevant to the current study design, provides several important observations relevant to the conduct of a large trial. They, along with other published data, demonstrate that ischemia can be suppressed by a number of approaches with potential for a clinical benefit, that better ischemia suppression will require a longer titration period and more aggressive therapy, and, provide a base for event rate estimates for proposed future interventional strategies. However, many uncertainties remain. Variable regimens, short duration and variable results coupled with insufficient sample size to resolve the survival benefits, severely limit the application of these strategies into a clinical practice. New anti-ischemic agents with more physiologically-desirable effects are also now available.

There have been widespread applications of both intensive medical and revascularization therapies targeting ischemia and dramatically changing clinical practice. Furthermore, revascularization is recommended by some on the basis of coronary anatomic findings alone, irrespective of presence of myocardial ischemia. However, there are no data from large randomized studies on the long term benefits and risks of aggressive medical vs revascularization therapies in patients with stable CHD to justify such aggressive intervention strategies. The question whether, in patients with stable CHD undergoing intense risk factor modification, ischemia should be treated aggressively, medically or with early revascularization, remains a pressing issue in clinical cardiology today.

Based on results from all these studies, it is logical to pose the hypothesis that intensive ischemic suppression, coupled with aggressive risk factor modification improves long-term prognosis in CHD patients with ischemia. Clearly, a large, long-term trial is needed to establish the long-term morbidity and mortality benefits, and quality of life and health care economics of practice-based anti-ischemic strategies, along with intensive modern medical therapy, of aggressive ischemia-targeted medical therapy, or an optimal revascularization strategy compared to symptom-oriented anti-ischemic therapy. The clinically important questions to be answered by the trial include in the selected group of patients with stable CHD who are prescribed intensive risk factor modification:

- does anti-ischemic therapy escalated to a maximum tolerated dose confer long-term morbidity and mortality benefits beyond anti-ischemic therapy targeted just for relief of angina
- does mechanical revascularization (PTCA or CABG) confer long-term morbidity and mortality benefits beyond anti-ischemic therapy targeted just for relief of angina, and
- what are the related costs and quality of life indicators?

The SOCRATES trial is designed to answer the above questions. It is anticipated that the results of the trial would significantly impact on clinical practice and health care costs.

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A. OBJECTIVES OF THE SOLICITATION AND BACKGROUND INFORMATION

Along the broad spectrum of ischemic heart disease, there is a consensus that in certain patient subgroups revascularization, with either percutaneous transluminal coronary angioplasty (PTCA) and/or coronary artery bypass surgery (CABG) is warranted, and that in other subgroups neither of these interventions is warranted. For other subgroups, evidence in favor of one or the other intervention is equivocal. Within the spectrum of stable coronary heart disease (CHD), the target population will be patients in whom there is equipoise between revascularization (PTCA and/or CABG) and modern, aggressive medical therapy.

The purpose of this program is to conduct a multicenter randomized trial addressing two key questions of therapeutic strategy in the management of CHD: first, in medical management, does anti-ischemic therapy escalated to a maximum tolerated regimen (conceptually to maximize pharmacologic suppression of all ischemia), confer long-term morbidity and mortality benefits beyond anti-ischemic therapy targeted just for relief of angina; and second, have advances in medical management of CHD (i.e., particularly aggressive lipid management, anti-thrombotic therapy, and life style risk factor modification), changed the threshold at which mechanical revascularization is

warranted? These questions will be addressed in patients with stable CHD and objective evidence of ischemia who are eligible for catheter-based revascularization (such as PTCA) or surgical revascularization with CABG. Functional status and health care costs related to the above strategies will also be assessed.

The SOCRATES trial will assess the benefits and risks of aggressive anti-ischemic strategies, in these stable CHD patients considered being at high risk for ischemic events, with respect to long term morbidity and mortality. The trial will also provide scientific insight into the role of ischemia in the long-term clinical outcome of CHD patients, and the cost and quality of life implications associated with proposed strategies. The information will provide a rational basis for safe and effective therapy for patients with stable CHD.

This program is based on the successfully conducted Asymptomatic Cardiac Ischemia Pilot (ACIP) study, but with significant modification into the protocol.

B. THE STUDY DESIGN

The following research design features constitute the draft protocol and serve as a guide to offerors. Offerors are expected to discuss their understanding of the study in their proposals and to present their own technical approach to accomplish the study objectives in accord with and as set forth in this draft protocol. Final drug regimens for medical strategies will be defined collaboratively during the implementation phase. The final protocol will be submitted to an expert review committee appointed by National Heart, Lung and Blood Institute (NHLBI).

This trial will involve patients with stable CHD and other eligibility and exclusion criteria detailed below, and in whom there is equipoise between medical therapy and revascularization (catheter-based or surgical). The choice between the potential revascularization approach that might be used, PTCA or CABG, will be made by physician and patient before randomization.

B.1. Objectives:

The trial primary objectives are to determine which of the three strategies--anti-ischemic therapy targeted just for relief of angina, anti-ischemic therapy escalated to a maximum tolerated dose, and mechanical revascularization (PTCA or CABG), each strategy accompanied by current aggressive medical management of CHD (namely, aggressive lipid management, anti-thrombotic therapy, and life style risk factor modification)--confers the best benefit. Thus, the primary aims of this program are to resolve whether:

a. anti-ischemic therapy escalated to a maximum tolerated dose confers long-term morbidity and mortality benefits beyond anti-ischemic therapy targeted just for relief of angina

b. mechanical revascularization (PTCA or CABG) confers long-term morbidity and mortality benefits beyond anti-ischemic therapy targeted just for relief of angina

c. mechanical revascularization (PTCA or CABG) confers long-term morbidity and mortality benefits beyond anti-ischemic therapy escalated to a maximum tolerated dose other objectives include:

d. to determine the relationship between the extent of ischemia reduction and the incidence of cardiac events,

e. to determine the “dose-response” relationship between heart rate reduction and ischemia and the incidence of cardiac events,

f. to determine the impact of different drugs (with different physiological profiles) on objective evidence of ischemia,

g. to determine prognostic significance of residual ischemia,

h. to determine comparative effectiveness of the 3 arms in their effect on asymptomatic ischemia

I. to determine the relationship(s) between ECG ischemia and major risk factors over a period of time,

j. and to determine functional status, quality of life, cost, and utilization of health resources with economic implications.

B.2. Sample size:

It is estimated that a total sample size of 6,000 patients will be needed (2,000 for each of the three treatment strategies) to assure at least 80% power for any two-group comparison with alpha = 0.05, to detect a difference of 20% or greater in the primary outcome, i.e., a survival free of myocardial infarction (MI). The yearly event rate in the angina-directed arm of ACIP was 6.245%, a rate comparable to those of other studies. This was reduced by 20%, to approximately 5% per year, to reflect more aggressive risk factor modification in SOCRATES. The five-year event rate for angina-directed arm of SOCRATES is therefore, assumed to be 22.6%.

Power is based on a two-stage procedure in which the three arms are first compared using an overall test at alpha = 0.05, and then pairwise comparisons are made at level alpha = 0.05, provided that the overall test is significant.

B.3. Eligibility Criteria

Patients eligible for the trial must exhibit:

-stable CHD, such as: a history of MI more than 1 month prior to enrollment; stable angina; asymptomatic CHD; or previous revascularization (at least 6 months earlier); and

-coronary artery disease amenable to revascularization, either by PTCA or CABG; and

-objective evidence of myocardial ischemia based on one of the following tests:

a) standard 12 lead ECG exercise stress (treadmill or bicycle) test: ≥ 1.0 mm ST-segment deviation from the baseline on exercise stress test using 12 lead ECG;

b) pharmacologic stress (adenosine or dipyridamole) coupled with perfusion scintigraphy (thallium or sestamibi): 1 or more scintigraphic perfusion defects (reversible or partially reversible) during imaging;

c) exercise or pharmacologic stress (dobutamine) coupled with 2-D echocardiography: 1 or more segmental wall motion abnormalities during 2-D echocardiography; or

d) exercise radionuclide ventriculography: 1 or more segmental wall motion abnormalities during exercise radionuclide ventriculography

However, ischemic changes on AECG alone will not be considered as sufficient evidence for this trial.

Patients with any of the following will be excluded:

a) class III or IV CHF at time of entry into study

b) left main stenosis > 50%

c) unable to be weaned from anti-ischemic medications for stress testing (except those who is post MI)

d) ineligible for revascularization

e) significant non-cardiac disease which would affect morbidity and mortality

f) persistent hypertension (BP > 180/100) while on drug therapy

B.4. Endpoints

a. The primary outcome of the trial will be survival free of MI.

b. Other outcomes of interest will include: cardiac symptoms requiring hospitalization, non-protocol revascularization, recurrent ischemia (symptomatic, on stress testing or AECG), quality of life, and cost. Patients, classified prior to randomization either as selected for potential PTCA or selected for potential CABG, will be also analyzed with respect to impact of the medical strategies within these two strata.

B.5. Duration of the trial:

The trial will consist of Implementation Phase (6 months), Recruitment Phase (24 months), Follow-up Phase (a minimum of 4 years with an average of 5-year follow-up), and Analysis Phase (6 months). The entire study duration is anticipated to be 7 years.

RANDOMIZED TREATMENT STRATEGIES

C. RANDOMLY ASSIGNED TREATMENT STRATEGIES

The patients will be first stratified on the basis whether PTCA or CABG had been selected as the potential (primary) revascularization procedure and then will be randomly assigned to one of three strategies: (1) protocol-defined angina-directed medical therapy, (2) protocol-defined intensive anti-ischemic medical therapy escalated to a maximum tolerated regimen to suppress all ischemia, or (3) revascularization. Each strategy will be accompanied by aggressive pharmacotherapy and risk factor modification.

C.1. Angina-Directed Medical Therapy

In this arm (“MED 1"), patients will receive the same regimens as those in the ischemia-directed medical therapy arm (see below), but when angina is controlled, escalation of therapy will continue with placebo.

C.2. Ischemia-Directed Medical Therapy

In this arm (“MED 2"), maximal medical therapy is protocol-directed toward abolishing all ischemia. The medical regimens will include combinations of several classes of drugs which have been shown to reduce ischemia, including long-acting calcium channel antagonists with and without negative chronotropic effect, beta blockers, nitrates, and angiotensin converting enzyme (ACE) inhibitors. “It is possible, within the study design, to consider a second randomization to different drug regimens”. The drug dosages would be escalated within a period of several weeks to the point of tolerance, i.e., the drugs and their dosages would be titrated until achieving resting heart rate of 50 bpm or systolic BP < 120 mm Hg, or until experiencing symptom-limiting side effects. The specific combinations of drugs and escalation schedules for the medical strategies will be finalized by the participating investigators.

C.3. Revascularization

The choice of the revascularization procedure, PTCA or CABG, will be made by the patient’s physician, and it will be made prior randomization. The goal of revascularization will be to achieve as complete revascularization as possible. It is anticipated that state-of-the-art techniques will be

employed. Patients with angina will be treated with the open label stepped-care regimen outlined below.

C.4. General Treatment Principles for Medical Anti-Ischemic Regimens

Anti-ischemic medical therapy for each patient will be along a protocol defined, stepped-care regimen, unless there is a specific reason to the contrary.

The regimens will differ somewhat according to absence or presence of prior history of MI, LV function and resting heart rate, with examples shown below. Within these grouping, there may be more than one regimen, e.g., a 6-step regimen involving drugs X and Y for the typical patient; another 6-step regimen involving the same drugs but at lower doses for a frail 120 lb patient; a 4-step regimen involving drugs Y and Z for the typical patient; etc.

The regimen selected will not be blinded, (unless that were to be a topic of a sub-study, as discussed below). Assignment to angina-directed anti-ischemic therapy (MED 1) or maximum tolerated anti-ischemic therapy (MED 2) is blinded. In both groups, patients will follow the same stepped-care approach, with escalation steps at intervals of several weeks to several months. When angina is satisfactorily controlled, patients in MED 2 will continue to receive the escalating regimen with active drug to the point of tolerance, or achieving a minimal heart rate (e.g., < 50 bpm) or systolic BP (e.g., < 120 mm Hg), or to the final step of the regimen. For patients in MED 1, when angina is satisfactorily controlled, active drug is continued and escalation continues using placebo in comparable manner. (Blinding of clinic staff as well as patient continues throughout the trial, but it is acknowledged that treatment-induced physiological effects and symptoms may result in some degree of unmasking.)

Patients who have no angina at the outset, will immediately start on active drug or placebo, according to their MED 2 or MED 1 assignment. Patients with a clinical indication for one of the drugs that is a part of the anti-ischemic regimen (e.g., a beta-blocker in a patient post myocardial infarction) will receive the indicated dose for that condition, and will then start or continue the escalation therapy with active drug and/or placebo, according to angina status and MED 2 or MED 1 assignment.

Unless required by symptoms, patients will be maintained on their drug therapy until completion of the trial. Patients who experience angina despite maximal medical therapy will be considered for revascularization.

Drugs with low side effects and once-a-day administration will be selected, wherever possible. The concept of a stepped regimen is illustrated by the following: Step 1 might be 50% of FDA-recommended maximum of Drug X. Step 2 might be 50% of FDA-recommended maximum of Drug X plus 50% of FDA-recommended maximum of Drug Y. Step 3 might be 100% of FDA-recommended maximum of Drug X plus 50% of FDA-recommended maximum of Drug Y. Step 4 might be 100% of FDA-recommended maximum of Drug X plus 100% of FDA-recommended maximum of Drug Y. This type of regimen assumes that a combination of agents optimizes the drugs' therapeutic effect while minimizing the side effects.

The specific stepped regimen for each of the six groups shown below is not yet fixed, and the possibility exists that within one or more groups there may be two different stepped care regimens, according to physician choice. Or this may be a formal sub-study with further randomization and blinding. For example, patients with EF $> 40\%$, no prior Q-wave MI, and resting heart rate > 60 bpm might be considered for sub-randomization for a heart rate lowering drug starting either with beta blocker or a calcium channel antagonist.

The strategy summarized above and the patient groupings summarized below are not final. However, proposers should be comfortable with the strategy, the patient groupings and the therapeutic options,

and they are expected to refine these plans. Proposers should not hesitate to also propose improved or alternate plans.

The following are illustrative examples:

No prior MI and heart rate > 60 bpm:

-long acting calcium channel antagonist with negative chronotropic effect (e.g., diltiazem, verapamil)

-nitrate (e.g., isosorbide 5-mono-nitrate)

-beta adrenergic antagonist (e.g., metoprolol, atenolol)

No prior MI and heart rate ≤ 60 bpm:

-long acting calcium channel antagonist without negative chronotropic effect (e.g., amlodipine, nifedipine)

-nitrate (e.g., isosorbide 5-mono-nitrate)

-beta adrenergic antagonist (e.g., metoprolol, atenolol)

Prior Q-wave MI and LVEF > 40%:

-beta adrenergic antagonist (e.g., metoprolol, carvedilol)

-long acting calcium channel antagonist without negative chronotropic effect (e.g., amlodipine)

-nitrate (e.g., isosorbide 5-mono-nitrate)

Prior Q-wave MI and LVEF ≤40%:

-ACE inhibitor

-beta adrenergic antagonist (e.g., metoprolol, carvedilol)

-nitrate (e.g., isosorbide 5-mono-nitrate)

Prior non-Q-wave MI and LV EF > 40%:

-long acting calcium channel antagonist with negative chronotropic effect (e.g., diltiazem, verapamil) or an agent with neutral chronotropic and inotropic effects (e.g., amlodipine)

-nitrate (e.g., isosorbide 5-mono-nitrate)

-beta adrenergic antagonist (e.g., metoprolol, carvedilol)

Prior non-Q-wave MI and LVEF ≤40:

-ACE inhibitor

-nitrate (e.g., isosorbide 5-mono-nitrate)

-beta adrenergic antagonist (e.g., metoprolol, carvedilol)

D. GENERAL MEDICAL THERAPY AND RISK FACTOR MANAGEMENT FOR ALL PATIENTS

All patients in all three strategies will receive intensive, state-of-the-art general medical therapy and aggressive risk factor management, as described below. A comprehensive risk factor assessment, including fasting blood tests, will be performed at the randomization visit, and each subject will receive a prescription based on his or her risk profile. The aims will be based largely on the AHA,

NCEP, and JNC VI and other guidelines50-52, as appropriate. All patients will receive therapy, unless contraindicated, with examples shown below:

1. Anti-thrombotic Therapy with aspirin (enteric-coated) 80-325 mg/day, or other appropriate antiplatelet agent;

2. Smoking Cessation: all smokers will receive counseling, using all appropriate strategies (e.g., nicotine replacement).

3. Lipid Management: based on a fasting lipoprotein profile obtained at baseline, 3, and 6 months, and every 6 months thereafter; the management will be based on the current NCEP guidelines, using a low-fat/low-cholesterol diet and drug therapy. The dietary goals will be: dietary cholesterol: $\leq$ 200 mg/day, total dietary fat: $\leq$ 30% calories, and saturated fat: $\leq$ 7% calories. The target of lipid interventions will be to achieve LDL cholesterol 80-100 mg/dL, plasma triglycerides $\leq$150 mg/dL, and HDL cholesterol $\geq$55 mg/dL in women and $\geq$45 mg/dL in men. It is anticipated that a HMG-CoA reductase inhibitor will be the preferred monotherapy, unless indicated otherwise by the patient's specific lipid profile.

4. Physical Activity: All patients will be provided with recommendations for a physical activity program, utilizing regular aerobic exercise and maximizing daily activities around the house/work, unless contraindicated. It is anticipated that the program will employ moderate intensity activities (e.g., walking, running, cycling) carried out for > 30 minutes at least 4-times per week.

5. Obesity Management: Ideal body weight will be based on the 1998 NHLBI Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults. Patients with > 120% of ideal body weight will receive appropriate dietary and physical activity regimens.

6. Hypertension Management: BP levels > 140/90 mmHg on 3 consecutive visits will be treated according to JNC VI guidelines.

7. Post-menopausal women: estrogen (adding progestin if uterus present) will be considered, unless indicated otherwise.

8. New Risk Reduction Therapies: It is anticipated that new therapies with proven safety and efficacy will be incorporated into the medical management plan for all arms of the trial as they become available.

E. FOLLOW-UP PROCEDURES

The follow up activities consist of both usual practiced-based medical management activities and protocol-derived activities.

E.1. Regular Follow-Up

All patients will have the same follow-up schedule, as outlined below and shown in the table 1:

a) clinic visits at 3, 6, and 12 months, and at 6 month intervals thereafter, to assess symptoms, control of ischemia, and compliance with therapy and risk factor modification;

b) rest ECG at 3 months, 6 months, 12 months, and annually thereafter;

c) ambulatory ECG at 3 months, 6 months, 12 months, and annually thereafter;

d) stress test (preferably exercise or the type of stress test done initially at baseline) at 6 months, 1 year and 3 years;

and in a subset of patients the following data will be collected:

e) quality of life assessments at 6 months, and annually thereafter;

f) cost and health resource utilization assessments annually.

E.2. Monitoring Compliance

Compliance with study medication will be assessed by querying patients about their pill taking regimen and consumption. The Drug Distribution Center, Clinical Network Centers, and the Clinical Data Coordinating Center will collaborate in assessing and assuring the highest level of compliance with the drug regimen according to the protocol assignment. Success at smoking cessation, weight control, exercise, and dietary and lipid levels modifications will be assessed using appropriate measures.

Table 1 below shows a schematic representation of the scheduled protocol evaluations. Certain evaluations, such as AECG, detailed quality of life, and costs may be done only in representative subset(s) of the patient population.

Table 1 Evaluations	Schedule of Evaluations (in months)											
	Baseline	**3**	**6**	**12**	**18**	**24**	**30**	**36**	**42**	**48**	**54**	**60**
+ Angiogram	X											
History & Exam	X	X	X	X	X	X	X	X	X	X	X	X
+ Lipid/Risk Profile	X	X	X	X	X	X	X	X	X	X	X	X
+ ECG	X		X	X		X		X		X		X
+ Stress test	X		X	X				X				
*Ambulatory ECG	X	X	X	X		X		X		X		X
*Quality of Life	X	X	X	X		X		X		X		X
*Costs	X			X		X		X		X		X

+ These evaluations are largely components of standard care; they are not directly reimbursable by the contract.
*These evaluations may be done in a subset(s) of study patients.

SECTION M—EVALUATION FACTORS FOR AWARD WITH TECHNICAL EVALUATION CRITERIA

GENERAL

Proposals submitted in response to this RFP will be reviewed by (1) a primary technical review group using peer review procedures under the auspices of Review Branch, DEA and (2) a secondary review group composed primarily of members of the DHVD, NHLBI professional staff.

Technical factors will be paramount in the decision to award a contract. Although technical factors are paramount in the decision to award a contract, price will be evaluated and is a substantial factor in the source selection decision. If two or more offerors are approximately equal in technical ability, then price may become paramount. In any event, the Government reserves the right to make an award to the best advantage of the Government, price and other factors considered.

This research project involves human subjects. NIH Policy requires that women, members of minority groups and their subpopulations, and children must be included in the study population of research involving human subjects, unless a clear and compelling rationale and justification is provided with respect to the health of the subjects or the purpose of the research.

Where inclusion of women, minority populations, and children are not feasible, a detailed rationale and justification for exclusion from the study population must be submitted with the technical proposal. The NHLBI will review the rationale to determine if it is appropriate with respect to the health of the subjects and/or the purpose of the research. If the rationale is not considered acceptable by the Government and you are included in the competitive range, you will be afforded the opportunity to further discuss and/or clarify your position during discussions or include women, minorities, and children in your Final Proposal Revision (FPR). If your exclusion position is still considered unacceptable by the Government after discussions, your proposal may not be considered further for award.

The factors to be evaluated are as follows:

No.	Criterion	Points
1.	Technical Qualifications of the Clinical Network Center (CNC): Adequacy of documentation of the proposed plans for the network to recruit and follow a minimum of 600 patients for an average of 5 years and minimum of 4 years, including screening, consent, and randomization to above stipulated treatment strategies. Adequacy of existing or prior collaboration with participating clinical units/clinical investigators within the proposed network.	**30**
2.	Knowledge and understanding of scientific issues: Suitability of the proposed final protocol, notably specific drug choices suitable for finalizing the protocol, plans for use of blinded anti-ischemic medications for the 2 medical strategies, and rationale and plans for potential for secondary randomization to various drug regimens in those assigned to medical strategies. Adequacy of understanding of treatment of coronary heart disease and myocardial ischemia, the rationale and design of the trial, and the proposed treatment strategies. Adequacy of the proposed methods to implement general medical therapy, including aggressive risk factor modification, and coordination of a follow-up of study patients, according to the protocol.	**30**
3 .	Personnel Qualifications: Suitability and availability of the proposed personnel, including specific competence and prior experience of professional, technical, and administrative staff pertinent to the operation of a CNC in multicenter randomized clinical trials in cardiovascular disease similar in complexity to SOCRATES. Medical and scientific expertise in cardiovascular medicine and therapy, and analysis and interpretation of medical data for purpose of ensuring and monitoring patient safety, ability to perform the protocol related work. Evidence of administrative and scientific leadership necessary for soliciting cooperation from participating clinical investigators and exercising appropriate leadership in matters of patient recruitment and patient management. Ability to take scientific leadership in data publication.	**20**
4.	Institutional Support, Corporate Facilities and Resources: Adequacy of the CNC institutions support to provide data on health care costs data related to the conduct of the SOCRATES trial. Adequacy of Institutional commitment to the program, and of the proposed facilities, equipment, and space for accomplishing the statement of work.	**20**
		Total: 100